# Distilling the essence of TMS-evoked EEG potentials (TEPs)

## A call for securing mechanistic specificity and experimental rigor

Siebner, Hartwig Roman; Conde, Virginia; Tomasevic, Leo; Thielscher, Axel; Bergmann, Til Ole

*Published in:*
Brain Stimulation

*DOI:*
10.1016/j.brs.2019.03.076

*Publication date:*
2019

*Document version*
Publisher's PDF, also known as Version of record

Brain Stimulation 12 (2019) 1051–1054

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

# Distilling the essence of TMS-evoked EEG potentials (TEPs): A call for securing mechanistic specificity and experimental rigor

Hartwig Roman Siebner [a, b, c, *], Virginia Conde [d], Leo Tomasevic [a], Axel Thielscher [a, e], Til Ole Bergmann [f, g, h]

[a] Danish Research Centre for Magnetic Resonance, Centre for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital Hvidovre, Denmark
[b] Department of Neurology, Copenhagen University Hospital Bispebjerg, Copenhagen, Denmark
[c] Institute for Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[d] Clinical Neuroscience Laboratory, Institute of Psychology, Norwegian University of Science and Technology, Trondheim, Norway
[e] Center for Magnetic Resonance, Department of Electrical Engineering, Technical University of Denmark, Kgs Lyngby, Denmark
[f] Deutsches Resilienz Zentrum (DRZ), Johannes Gutenberg University Medical Center, Mainz, Germany
[g] Department of Neurology & Stroke, and Hertie Institute for Clinical Brain Research, Eberhard Karls University of Tübingen, Tübingen, Germany
[h] Institute for Medical Psychology and Behavioral Neurobiology, Eberhard Karls University of Tübingen, Tübingen, Germany

ARTICLE INFO

*Article history:*
Received 19 March 2019
Accepted 23 March 2019
Available online 2 April 2019

*Dear Editor*

Using realistic sham stimulation, we have shown that transcranial magnetic stimulation (TMS) produces significant off-target excitation of the peripheral nervous system, even when applying state-of-the-art procedures to attenuate peripheral co-activation [1]. The peripherally evoked potentials (PEPs) strongly resembled TMS-evoked potentials (TEPs) [1]. Our study prompted a letter to the editor in the Brain Stimulation journal, signed by many researchers using TEP recordings [2]. While Belardinelli et al. [2] appreciate our work as a "valuable reminder to the TMS-EEG community", they also criticize our experimental approach. We would like to thank Belardinelli et al. [2] for taking up the debate and are grateful for the possibility to reply.

Belardinelli et al. [2] claim that the evoked responses obtained from both real TMS and sham conditions were "substantially different from the TEPs reported in many of the previous studies". We respectfully disagree. Indeed, most published TMS-EEG papers did report TEPs with amplitudes and shapes comparable to the ones we observed after both, real and realistic sham TMS. This was also the case for the latency and potential distribution of the N100 peak, a commonly analysed component of the TEP. A PUBMED literature search (02nd March 2019), using the search terms "TMS", "EEG", and "N100", yielded 20 TMS-EEG studies which were published between 2017 and 2019 and targeted frontal or parietal areas (Suppl. Table). The spatiotemporal properties of the TEPs and PEPs which we recorded in our study [1] are very similar to the TEPs reported in most of these publications, showing small early TEP components with amplitudes $\leq 5\mu V$ and similar N100 properties. Fig. 1 gives an illustrative example, showing that our TEPs and PEPs reproduced the TEPs published by Chung and colleagues [3] who targeted the same medial prefrontal area [1].

Belardinelli et al. [2] characterize the stimulation intensity used in our study as "insufficient", although our electrical field modelling confirmed the induction of electrical currents in extended parts of the targeted gyral crown that were clearly above the threshold for exciting cortical neurons [1]. Stimulus intensities in TMS-EEG studies are often expressed in percentage of resting motor threshold (RMT) over the primary motor hand area (M1-HAND). We did not assess RMT in our study, but to enable comparison, we

* Corresponding author. Danish Research Centre for Magnetic Resonance (DRCMR), Centre for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital Hvidovre, Kettegård Allé 30, 2650, Hvidovre, Denmark.
*E-mail address:* hartwig.siebner@drcmr.dk (H.R. Siebner).
*URL:* http://www.drcmr.dk/siebner

https://doi.org/10.1016/j.brs.2019.03.076

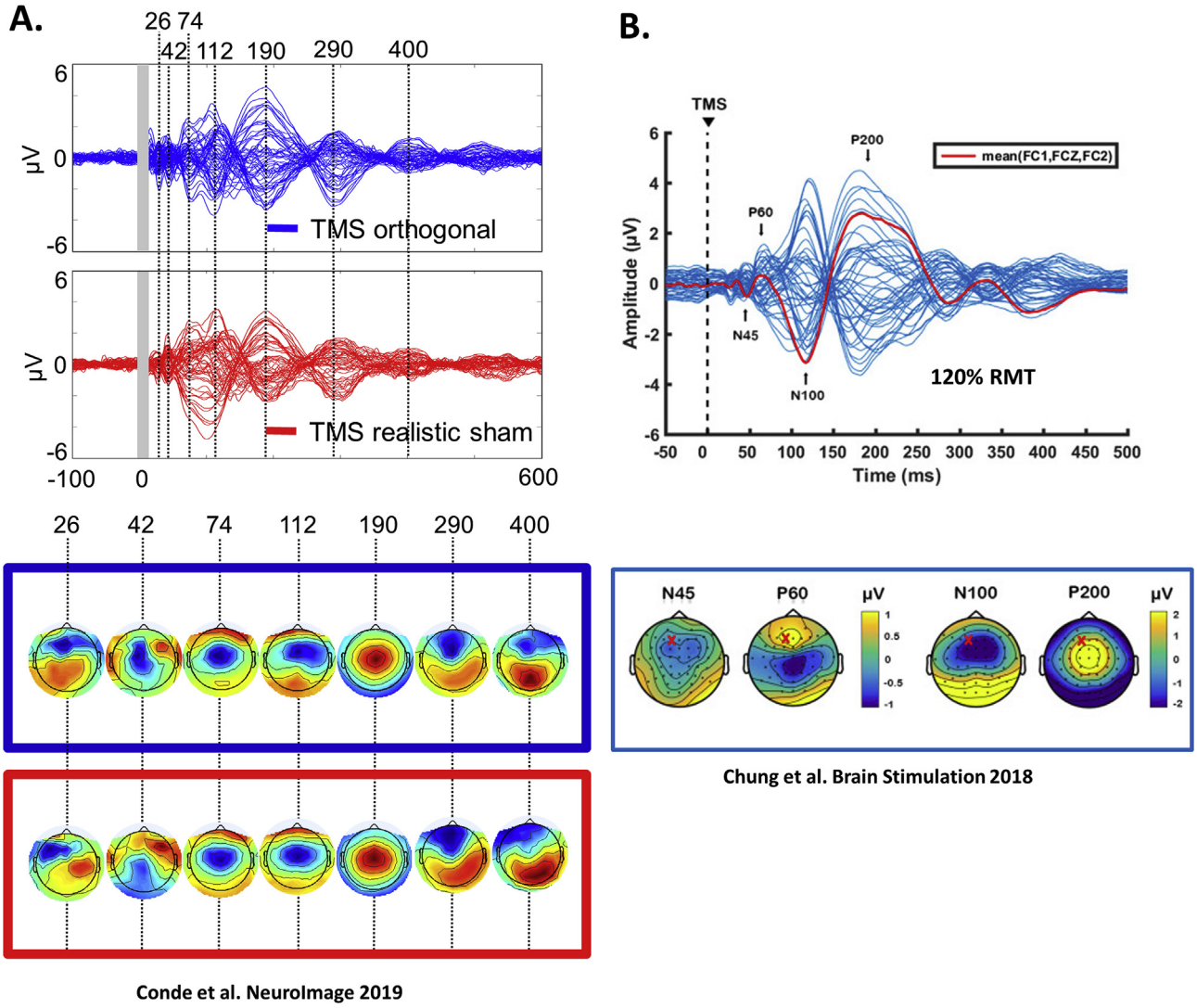


**Fig. 1.** Panel A shows the group average of frontal TEPs and PEPs published by Conde et al. (2019) [1]. Panel B gives the group average of frontal TEPs from a recent study by Chung et al. (2018) that targeted the same frontal cortical region [3]. The upper panels represent butterfly plots of the evoked potentials for each electrode. The lower panels are topographical plots illustrating the spatial potential distribution of the evoked potentials at relevant peaks. Please note that the TEPs produced in both studies are highly comparable.

now assessed RMT using our original setup [1] in 10 healthy young volunteers. Mean RMT was 63% (53–75%) of maximal stimulator output (MSO) when targeting left M1-HAND. The RMT intensities match the range of stimulus intensities used in our recent TMS-EEG study [1], namely 59% (40–72%) of MSO for medial prefrontal TMS and 66% (60–72%) of MSO for medial parietal TMS. We therefore argue that our TMS-EEG study employed stimulus intensities around RMT that are capable of focally exciting the cortical target site and are comparable to the stimulus intensities (80–120% RMT) commonly used in many TMS-EEG studies (Suppl. Table).

Belardinelli et al. [2] correctly state that the noise masking procedure may have not been efficient given our participants report hearing the click sound even with noise masking, when using sound levels still tolerable by the participants. Two previous studies proved that state-of-the-art noise masking strategies may not adequately supress cortical auditory processing when the coil touches the head and a layer of foam is placed in-between coil and skin, as indexed by a residual N100–P180 complex [4] or residual perception of the acoustic clicks [5]. We are concerned that residual auditory input may be very common, yet unexplored nor properly reported in TMS-EEG studies. But even if complete noise masking could be achieved, concurrent somatosensory stimulation through mechanoreceptors and axons in the skin, neuroforamina, and dura mater would still cause significant somatosensory co-stimulation during TMS.

We therefore insist on the fact that the stimulus intensities as well as the spatiotemporal TEP patterns reported in our study [1] are representative for the TMS-EEG literature, and that stimulus intensities were sufficiently effective to induce focal cortex stimulation. Although we correctly applied state-of-the-art procedures of noise masking and foam padding, peripheral off-target stimulation produced PEPs that closely matched the TEPs evoked by real TMS in our study [1] but also reproduced the TEP features reported in most TMS-EEG studies (Fig. 1, Suppl. Table). Our results call for experimental procedures that effectively handle inherent off-target stimulation in TMS-EEG studies. We advocate for a routine implementation of control stimulation conditions that match as much as possible the multisensory perception evoked by the specific TMS-EEG set-up and stimulus intensity, complemented by in-depth assessment of subjective auditory and somatosensory percepts.

It is possible that TMS-EEG settings using higher simulation intensities (>100 V/m, >130% of RMT) or larger coils may result in a

more favourable ratio between on-target (transcranial) and off-target (peripheral) brain activation. We did not assess the impact of PEPs on TEPs at high TMS intensities (>100 V/m, >130% of RMT) or when using larger TMS coil diameters, which can be used to produce stronger and larger electric fields and thus a stronger synchronized response in larger neuronal populations. A stronger focal brain response and trans-synaptic spread to connected brain regions will increase the true transcranial component of the TEP. At the same time, higher stimulation intensities and larger coils will also cause stronger peripheral off-target stimulation, increasing the absolute contribution of the PEPs. Moreover, even with a transcranial response being much higher than PEP contribution, it is not possible to know which of the two has the major contribution in evaluating statistical differences between two conditions or experimental groups. Therefore, an appropriate sham control stimulation should be employed to determine the relative contribution of PEPs when TMS is applied at high stimulus intensities or through less focal stimulating coils.

Two recently published studies aimed at identifying the multisensory contribution to the TEP for TMS of M1-HAND [5,6]. Gordon et al. [5] positioned the coil positioned 20 cm above the head, not adjusting the sound levels by the distance and preventing bone conduction, which is the main contributor to TMS-evoked auditory potentials [7]. Cutaneous electrical stimulation was comparably weak (2.50 mA), i.e., approximately a quarter of the intensity we had to apply to match the sensation evoked by real TMS. Since sham stimulation did not sufficiently match auditory and somatosensory co-stimulation evoked by real TMS, it is not surprising that this non-realistic control stimulation elicited PEPs of much smaller amplitudes than "real" TEPs [6]. In principle, the insertion of a rigid cube (e.g., from plastic or Plexiglas) in between coil and head would be a step in the right direction, as such a cube transmits some of the TMS-evoked sound waves and thereby induces auditory input via bone conduction and somatosensory input via mechanoreceptors in the skin. However, bone conduction via such a cube is still reduced relative to direct contact of coil and head [7], and somatosensory stimulation via direct peripheral/cranial nerve stimulation is lacking. Using a sham stimulation similarly to Herring et al. [8], Biabani and colleagues [5] applied peripheral magnetic stimulation over the shoulder region, to produce auditory and somatosensory input of comparable subjective intensity. Shoulder stimulation does not result in a completely realistic sham because of a mismatch in auditory stimulation (i.e., less bone conduction) and different topographies and latencies of shoulder- and scalp-evoked potentials. Nonetheless the study replicated the marked contribution of PEPs to TEPs [5].

Our study calls for the implementation of truly realistic sham conditions as an integral part of future TMS-EEG studies and assessment of individual levels of perception of multisensory stimuli that are an integral aspect of TMS. Given the substantial contribution of PEPs to TEPs, one cannot claim mechanistic specificity regarding transcranial target engagement and modification without implementing an appropriate peripheral control stimulation in the experimental design of all TMS-EEG studies. The TMS-EEG field may take inspiration from "virtual lesion" studies in which the effects of peripheral co-stimulation are routinely considered when interpreting the behavioural effects of TMS on task performance [9,10]. We would like to conclude by emphasizing our strong support for the suggestion by Belardinelli et al. [2] to jointly define standard procedures that will secure unambiguous results in future TMS-EEG studies.

**Supplementary Table**

The table summarizes 20 TMS-EEG studies which were published from 2017 to 2019 and targeted frontal or parietal areas. The studies were revealed by a PUBMED literature search (02nd March 2019), using the search terms "TMS", "EEG", and "N100". Of note, the search was not designed to capture all TMS-EEG studies published in that period, but to identify those studies in which the N100 was a relevant outcome measure. The N100 is a commonly analysed component of the TEP in TMS-EEG studies, and it was also a prominent component of the PEPs recorded in our study.

Although the 20 studies differed in many experimental details, they consistently reported TEPs of similar amplitude and shape as the TEPs and PEPs reported in our realistic sham TMS-EEG study. Apart from study [12] which evoked MEPs, all studies reported early TEP components with amplitudes $\leq 5\mu V$ in the 70 ms time window after the TMS pulse. All listed studies reported a N100 component of similar amplitude and latency as the PEP N100 component reported in our study.

N = number of participants per study; Target sites: DLPFC: Dorsolateral prefrontal cortex, M1-HAND: Primary motor hand area; F1, F3, F5 refer to the electrode position according to the international 10–20 system. Stimulus intensities were adjusted based on TMS over the M1-HAND. Intensities were either individually adjusted to an intensity that corresponded to a certain percentage of resting motor threshold (%RMT) or an intensity that evoked a mean amplitude of the motor evoked potential (1mV MEP).

None of the studies included a sham condition in the experimental design apart from the study by Du et al. [19] which used a sham TMS-EEG condition with the coil centred above $P_Z$, 1–2 cm above the skull, tilted at 90°, and discharged at 120% of RMT. This sham control neither caused auditory stimulation via bone conduction nor induced relevant somatosensory stimulation.

## Competing interests

Hartwig R. Siebner has received honoraria as speaker from Novartis, Denmark and Sanofi Genzyme, Denmark, as consultant from Sanofi Genzyme, Denmark, and as senior editor (NeuroImage) from Elsevier Publishers, Amsterdam, The Netherlands. He has received royalties as book editor from Springer Publishers, Stuttgart, Germany and has received research funding from Biogen-idec, Denmark. The other authors report no conflict of interests.

## Acknowledgements

Hartwig R. Siebner and Axel Thielscher received support from Novo Nordisk Fonden (Synergy grant "Biophysically Adjusted State-Informed Cortex Stimulation", NNF14OC0011413). HRS holds a 5-year professorship in precision medicine at the Faculty of Health Sciences and Medicine, University of Copenhagen which is sponsored by the Lundbeckfonden (R186-2015-2138).

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.03.076.

## References

[1] Conde V, Tomasevic L, Akopian I, Stanek K, Saturnino GB, Thielscher A, et al. The non-transcranial TMS-evoked potential is an inherent source of ambiguity in TMS-EEG studies. Neuroimage 2019;185:300–12.

[2] Belardinelli P, Biabani M, Blumberger DM, Bortoletto M, Casarotto S, David O, et al. Reproducibility in TMS-EEG studies: a call for data sharing, standard procedures and effective experimental control. Brain Stimul 2019;(19): 30041–5. https://doi.org/10.1016/j.brs.2019.01.010. Jan 19. pii: S1935-861X.

[3] Chung SW, Rogasch NC, Hoy KE, Fitzgerald PB. The effect of single and repeated prefrontal intermittent theta burst stimulation on cortical reactivity and working memory. Brain Stimul 2018;11(3):566–74.
[4] ter Braack EM, de Vos CC, van Putten MJ. Masking the auditory evoked potential in TMS-EEG: a comparison of various methods. Brain Topogr 2015;28(3):520–8.
[5] Biabani M, Fornito A, Mutanen TP, Morrow J, Rogasch NC. Characterizing and minimizing the contribution of sensory inputs to TMS-evoked potentials. BioRXiv 2018. https://doi.org/10.1101/489864.
[6] Gordon PC, Desideri D, Belardinelli P, Zrenner C, Ziemann U. Comparison of cortical EEG responses to realistic sham versus real TMS of human motor cortex. Brain Stimul 2018;11. 1322e30, https://doi.org/10.1016/j.brs.2018.08.003.
[7] Nikouline V, Ruohonen J, Ilmoniemi RJ. The role of the coil click in TMS assessed with simultaneous EEG. Clin Neurophysiol 1999;110(8):1325–8.
[8] Herring JD, Thut G, Jensen O, Bergmann TO. Attention modulates TMS-locked alpha oscillations in the visual cortex. J Neurosci 2015;35(43):14435–47.
[9] Sawaki L, Okita T, Fujiwara M, Mizuno K. Specific and non-specific effects of transcranial magnetic stimulation on simple and go/no-go reaction time. Exp Brain Res 1999;127(4):402–8.
[10] Duecker F, Sack AT. Rethinking the role of sham TMS. Front Psychol 2015;6:210.